Clinical Diagnostic Exome Sequencing in Dystonia:
The Challenges of Genetic Testing for Complex Conditions

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**BACKGROUND**
- Dystonia is a group of clinically and genetically heterogeneous disorders characterized by involuntary muscle contractions producing abnormal postures and/or repetitive movements (1).
- Due to the diverse clinical manifestations in dystonia, diagnosis can be challenging, but if a genetic etiology can be determined, targeted therapies can be initiated and symptoms may be reduced (2).
- The continual discovery of new genetic etiologies for dystonia can aid in treatment but also underscores the complexity of genetic testing.
- With the ability to re-analyze and test for newly reported or novel genetic etiologies, Diagnostic exome sequencing (DES) may have clinical utility in the treatment of dystonia.

**METHODS**
- In an unselected cohort of 189 patients with reported dystonia referred for DES who then underwent characterized and/or novel candidate gene analysis (proband with informative family members in which novel genetic analysis was requested), the overall results categories were determined according to predefined diagnostic variant assessment criteria (3).
- Available clinical information was reviewed, due to the clinical complexity of distinguishing between dystonia and pseudo dystonia with record review, cases with dystonic posturing or dystonia like symptoms were also included in analysis.

**CLINICAL CHARACTERISTICS OF PROBANDS WITH REPORTED DYSTONIA UNDERGOING GENETIC TESTING**

**GENE FINDINGS**

**TAKE-HOME POINTS**
- Genetic testing for dystonia is important as the diagnosis of genetic etiologies in several genes can lead to therapeutic decisions.
- While panel specific testing may be helpful in certain cases, DES has the advantage of re-classification for new genes in this rapidly changing field.
- There are also advantages as many cases are not straightforward. Detection rates of individuals that present with dystonia or potential dystonia are similar to individuals with other genetic conditions undergoing DES; many having previous genetic testing.
- While some of these conditions expand upon the known phenotypes of conditions (as is common in dystonias), other may be explained by complex patients with multiple findings may potentially have a psychogenic dystonia.
- Genetic testing for dystonia continues to be challenging, but DES has unique advantages that align well with the ever expanding list of genes underlying this disorder; the complexity of clinical diagnosis and precision medicine obtained by these test results.

**REFERENCES**

**DETECTION RATES OF INDIVIDUALS WITH DYSTONIA**

- Positive/Likely Positive: 22%
- Uncertain: 26%
- Candidate/Suspected: 12%
- Negative: 59%

**AGE OF ONSET OF DYSTONIA SYMPTOMS**

- Infancy (birth - 2 yr): 55, 29%
- Childhood (3-12 yr): 44, 24%
- Adolescence (13-20 yr): 6, 3%
- Early adulthood (21-40 yr): 6, 3%
- Late adulthood (40 yr): 8, 4%
- Unspecified: 70, 37%